## 1.0 PURPOSE

This policy defines the minimum requirements for on-site monitoring of Division of AIDS (DAIDS) funded and/or sponsored clinical trials to ensure consistency, acceptability of the research data, and the safety of the participants.

## 2.0 SCOPE

This policy applies to all sites conducting DAIDS funded and/or sponsored clinical trials either within or outside of an HIV/AIDS Clinical Trials Network.

## 3.0 BACKGROUND

The monitoring of clinical sites is one element of a larger program of clinical trials oversight developed by the Division of AIDS (DAIDS) to fulfill its responsibilities to:

- Ensure the safety and welfare of participants
- Maximize adherence in the conduct of clinical research trials
- Verify data quality, completeness, and accuracy
- Assure that clinical trials continue no longer than necessary to meet their primary scientific objectives

The overall monitoring program involves careful review of proposed clinical trials, a requirement for meaningful local quality control/quality assurance programs, site performance evaluation systems, structured interim reviews of trial data, and appropriate site monitoring. Data reviews, including individual adverse event reports as well as summaries of both safety and efficacy data, necessarily presume that captured data are accurate and essentially complete. Clinical site monitoring is required to supply empirical evidence regarding that presumption.

In addition to FDA regulated Investigational New Drug (IND) studies, DAIDS supports clinical research that may involve approved study agents used in new settings or treatment strategies or other interventions that may involve substantial risks to participants. This relative risk, as well as the scope and complexity of the research will influence the type and extent of monitoring required. The following criteria may be used to guide these decisions at the Program level including whether monitoring will be supplied through DAIDS, a pharmaceutical sponsor, a network, and/or an investigator.

## 4.0 DEFINITIONS

**DAIDS Monitor** - a qualified monitor who is contracted by and reports to DAIDS and uses DAIDS SOPs and reporting procedures.

**Independent Monitor** - a qualified individual supplied by the pharmaceutical sponsor, or contracted by the network or investigator from an organization that utilizes its own SOPs and reporting procedures to provide independent clinical trial oversight. The independent monitor may not be employed directly by the network, clinical trial team, or any clinical research site.

**Internal Monitor** - a qualified employee of the investigator or the network who provides oversight of the clinical trial.

For additional definitions see DAIDS glossary.

## 5.0 RESPONSIBILITIES

Clinical site monitors will conduct on-site review of source documents, participant records, regulatory files, facilities, laboratories and pharmacies. Detailed reports will be provided to the Principal Investigator (PI) as well as to DAIDS staff.

- The PI is ultimately responsible for the correction of deficiencies identified during a monitoring visit.
- DAIDS Program staff are responsible for reviewing monitoring reports and ensuring that the PI has a plan of action for correction of deficiencies.

## 6.0 POLICY

### 6.1 CLINICAL TRIALS CONDUCTED UNDER AN IND (FDA regulated)

6.1.1 All clinical research trials for which DAIDS is the IND-holder must be monitored by a DAIDS monitor. The extent of monitoring will be related to the size, risk and complexity of the trial and may change depending upon the status of the trial, the needs of DAIDS and the performance of the site.

6.1.2 All clinical research trials for which another entity is the IND-holder must be independently monitored. The monitoring may be conducted either by a DAIDS monitor or by a contractor obtained independently by the IND-holder or supplied by a pharmaceutical sponsor. In the latter case, the

contractor or pharmaceutical sponsor monitors must be identified and a monitoring plan approved by DAIDS prior to enrollment.

## 6.2 SITE MONITORING REQUIREMENTS FOR NON-IND CLINICAL TRIALS

6.2.1 Non-IND clinical trials must be monitored, but in some cases, internal monitoring will be permitted. The final decision regarding monitoring of a non-IND trial will be made by the Program Officer in consultation with the Office for Policy in Clinical Research Operations (OPCRO). The monitors must be identified and the plan for internal monitoring must be approved by DAIDS prior to enrollment.

## 6.3 MINIMUM STANDARDS FOR SITE MONITORING OF CLINICAL TRIALS

Note: *In all cases, DAIDS reserves the right to conduct or delegate on-site monitoring for all clinical research trials as needed to ensure the safety of participants and integrity of trial data.*

6.3.1 Selection and Qualifications of the Clinical Site Monitor

6.3.1.1. Contract Research Organizations must use monitors who meet the qualifications set forth in their respective contracts with DAIDS, unless exceptions are specifically granted by the DAIDS Monitoring Contract Project Officer.

6.3.1.2. If site monitors are provided or contracted by an entity other than DAIDS (or if a site or investigator is permitted to use internal monitors), the monitor(s) must be approved by the Clinical Research Resources Branch (CRRB) in OPCRO.

6.3.1.3. In general, monitors should be qualified by experience and training and will have a Bachelor's/University degree or equivalent in nursing, pharmacy, biology, or other biomedical sciences.

6.3.1.4. Monitors should have experience in clinical research, and preferably have experience in site monitoring clinical trials, implementing HIV/AIDS studies, working with community and/or hospital clinic or laboratory staff,

teaching clinical staff, and/or performing quality assurance audits.

Note: *Exceptions to these qualifications will require review and approval from the DAIDS Project/Program Officer.*

6.3.2 Frequency of site visits

6.3.2.1. The DAIDS Monitoring Contract Project Officer, in consultation with the monitoring contractor and the Program Officer, will determine the frequency of site visits based on the risk, size, and complexity of the trial. All IND trials will be monitored no less than twice per year and at least one of those monitoring visits will be conducted by an independent or DAIDS monitor.

6.3.2.2. For some non-IND trials, DAIDS may permit the PI to sponsor internal monitoring. In the case of a non-IND trial of ***minimal*** risk, DAIDS may permit all monitoring to be done by internal monitors.

6.3.3 Review of Site Regulatory Files

6.3.3.1. At a minimum, the complete regulatory file must be reviewed once per year.

6.3.4 Assessment of Pharmacy Operations

6.3.4.1. The DAIDS Project Officer for the monitoring contract will, in consultation with the monitoring contractor and DAIDS Pharmaceutical Affairs Branch (PAB), determine the frequency of pharmacy visits for IND and non-IND trials based on the risk, size, and complexity of the trial. At a minimum, the operations of the investigational pharmacy will be assessed once per year by a DAIDS monitor.

6.3.5 Review of Clinical Research Participant Records at Each Visit

*Note: A sufficient number must be reviewed to constitute an adequate sample of the total enrollment.*

6.3.5.1. Original signed informed consent documents will be reviewed for compliance with Good Clinical Practice (GCP) and the DAIDS SOP for source documentation.

6.3.5.2. Original source documentation will be reviewed to verify all inclusion/exclusion criteria and for compliance with protocol requirements and the DAIDS policy for source documentation.

6.3.5.3. Individual participant's original source documents will be reviewed and compared to the protocol requirements and the completed case report forms.

6.3.5.4. Factors in determining what constitutes an "adequate sample" may include (but are not limited to): study risk, size, complexity, age of participants, experience of clinical site staff, and findings from prior site monitoring visits. The number of records to be reviewed will be determined by DAIDS Program/Project officers, in consultation with the monitoring contractor (if applicable), and defined in the monitoring plan.

6.3.6 Clinical Site Monitoring Visit Reports

6.3.6.1. Written reports of the reviews of research records, regulatory files, and site, laboratory and pharmacy operations must be submitted to DAIDS by the designated monitor according to timelines defined in the monitoring plan.

6.3.6.2. Prior to distribution, information that could lead to unblinding will be removed from the report. Information that is removed from a report due to potential for unblinding, such as, but not limited to, physical inventories, is to be submitted in a separate document to DAIDS PAB.

6.3.6.3. Distribution of visit reports will include (but not be limited to): DAIDS Monitoring Contract Project Officer, DAIDS responsible Program Officer(s), Regulatory Affairs Branch Chief, PAB Chief (if applicable), Principal

Investigator, and the Medical Officer for a study as requested or as necessary.

6.3.7 Issues or Findings Requiring Expedited Reporting

6.3.7.1. Suspected instances of scientific misconduct will be immediately reported directly to the DAIDS CRRB Chief, the DAIDS Monitoring Contract Project Officer (if applicable), and Program Officer(s) responsible for the site and for the study at DAIDS.

6.3.7.2. Reporting of other critical issues or findings will be expedited according to the seriousness of the finding. In general, these issues/findings should be reported to DAIDS as soon as possible.

## 7.0 REFERENCES


U.S. Code of Federal Regulations 21 CFR 312.56: Review of Ongoing Investigations
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr312_05.html

FDA Guideline for the Monitoring of Clinical Investigations (November 1998)
http://www.fda.gov/ora/compliance_ref/bimo/clinguid.pdf

DAIDS Policy
Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials

## 8.0 INQUIRIES

Questions and comments regarding this policy may be directed to:

NIAIDOPCROPOLICYGROUP@mail.nih.gov

## 9.0 AVAILABILITY

This policy is available electronically at the following URL:
http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Default.htm

The signed original is maintained in the OPCRO policy office.

## 10.0 CHANGE SUMMARY

| Version # | Date | Replaces | Date of Revision | Rationale for Revision/Retirement |
|---|---|---|---|---|
| 1.0 | 14 JUL 06 | N/A | N/A | N/A |

## 11.0 APPENDICES

None.

## 12.0 APPROVAL

| | Signature | Program/Branch | Date |
|---|---|---|---|
| Authorized By: |  <br>Richard Hafner, MD<br>Director | Office for Policy in Clinical Research Operations | July 14, 2006 |